## REMARKS

After entry of the amendments, claims 1, 4, 17-18, and 26-28 are pending in the application. Claims 2 and 25 have been canceled. Claim 28 has been added. Group III claims 1, 4, 17-18, and 26-27, drawn to methods for delivering a synthetic analog of a human growth hormone releasing hormone, are under consideration, and Group I claims 1, 4 and 17-21, and Group II claims 1, 4, 17-18, and 22-24, drawn to methods for delivering synthetic analogs of a human granulocyte colony stimulating factor, and a human parathyroid hormone, respectively, have been withdrawn from further consideration.

New claim 28 depends from claim 1 indicates that the parent polypeptide is human growth hormone releasing hormone. Support for this amendment is found in originally filed claim 25. Claims 1, 18, 26, and 27 have been amended herein. Claim 18 has been amended to include a period at the end of the claim. Claim 27 has been amended to correct the spelling of "histidine." Claim 1 has been amended to indicate that the pharmaceutical parent polypeptide agent includes at least one threonine residue and that the synthetic analog of the pharmaceutical parent polypeptide agent has at least one threonine residue replaced with histidine. Support for this amendment is found on page 8, line 13 to page 9, line 3 of the specification and in original claim 2. Additionally, claim 26 has been amended into independent form. Applicant submits that no new matter has been added by these amendments.

Claims 1, 4, 17-18, and 26-27 stand variously rejected as follows. In view of the amendments and the arguments below, Applicant respectfully requests reconsideration on the merits of the application and allowance of the claims.

Claim Objections

Claims 18 and 27 stand objected to for informal matters. Claim 18 has been amended to end with a period, and the term "histadine" in claim 27 has been replaced with "histidine." Applicant submits that these amendments have corrected the informalities and respectfully requests that the objection to the claims be withdrawn.

Comment on the scope of "human growth hormone releasing hormone" in claims 25-27

On page 5, paragraph 16 of the Office Action the Examiner indicates that the specification specifically defines "human growth hormone releasing hormone" polypeptide as being the

polypeptide of SEQ ID NO:8. While the specification makes it clear that SEQ ID NO:8 is clearly an example of "human growth hormone releasing hormone," the specification also indicates that such a sequence is merely an illustrated example of an analog of "human growth releasing hormone." *See* page 12, lines 28-31 of the specification. Applicant submits that the Examiner's contention that the term "human growth releasing hormone" is solely restricted to SEQ ID NO: 8 is unduly limiting given applicants disclosure in the specification that it is simply one analog of a "human growth hormone releasing hormone." One of ordinary skill in the art would contemplate that other analogs of "human growth releasing hormone" would also be included as well as SEQ ID NO: 8.

Rejections of claims under 35 U.S.C. § 112, first paragraph

Claims 1, 4, 17, and 18 stand rejected under 35 U.S.C. § 112, first paragraph, for lacking sufficient enablement. Applicant submits that claims 1, 4, 17, and 18 as amended herein satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph.

Enablement is properly determined on the basis of whether the specification contains "sufficient information . . . to enable one skilled in the pertinent art to make and use the claimed invention." MPEP § 2164.01. Thus, one must also take into consideration the knowledge of one of ordinary skill in the art, not just what is literally disclosed in the specification. *Id.*; *see also In re* Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991) ("A patent need not teach, and preferably omits, what is well known in the art."). Furthermore, "[t]he determination of what constitutes undue experimentation . . . is not merely quantitative." *Ex parte* Jackson, 217 USPQ 804 (BPAI 1982) ("a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed").

Claim 1, as amended, recites:

> "A method for delivering a pharmaceutical polypeptide agent through a body surface, comprising the steps of:
>
> (a) providing a synthetic analog of a pharmaceutical parent polypeptide agent, wherein the pharmaceutical parent polypeptide agent includes at least one threonine residue and the synthetic analog of the pharmaceutical parent polypeptide agent has at least one threonine residue replaced with histidine; and

(b) delivering the analog through the body surface by electrotransport." *See* claim 1, emphasis added

The present specification, combined with the knowledge of one of skill in the art, provides ample guidance to enable one skilled in the art to make a synthetic analog of a pharmaceutical parent polypeptide agent having at least one threonine residue replaced with histidine, and to deliver the synthetic analog through a body surface.

As to providing a pharmaceutical parent polypeptide agent having at least one threonine residue replaced with histidine, the specification specifically points out that such synthesis methods are conventional and are known to one of ordinary skill in the art. By way of example, the specification specifically points out synthesis methods taught by R.B. Merrifield et al., *Biochemistry*, vol. 21 (1981) 5020; M. Bodansnsky, *"Principles of Peptide Synthesis,"* Akad.-Verlag (1994); J.M. Stewart et al. "*Solid Phase Peptide Synthesis,"* Freeman (1969); Houghten et al., *Proc. Natl. Acad. Sci. U.S.A.,* vol. 82 (1985) 5131-5135; Houghten et al., *Peptide Chemistry,* (1987) 295-298; U.S. Patent No. 4,631,211, all of which were incorporated by reference in the specification of the application.

The specification further teaches that such histidine modified polypeptides provide a polypeptide with increased electrophoretic mobility due to the higher net positive charge of the peptide. The specification indicates that:

"the replacement of His for....Thr [i.e., threonine] results in increased hydrophilicity of the analog compared to the parent drug or unmodified polypeptide due to the positive charge on the imidazole ring and increased electrophoretic mobility due to the higher net positive charge. The result is that the analog exhibits increased transdermal electrotransport flux compared to the parent drug." *See* page 8, line 29 – page 9, line 3 of the specification, emphasis added.

It is a result of physical law that increased charges increases the electrical attraction and repulsion between ions and electrodes. One of ordinary skill in the art would know from the disclosure of the specification that replacing Thr by His will similarly result in increase + charge and increased electrotransport flux. Applicant, therefore respectfully submits that claim 1, as amended, is adequately enabled by the specification.

Claim 4, which depends from claim 1, recites:

"The method of claim 1, wherein the analog exhibits at least about the same type

and amount of biological activity as the parent polypeptide agent." *See* claim 4.

The specification indicates that:

> "Replacing His for Gln, Asn or Thr in accordance with the present invention is viewed as a "conservative" modification or derivatization of a polypeptide or protein. By this it is meant that the hydrophobicity, net charge at physiological pH, volume, and hydrogen bonding capacities of the parent polypeptide or protein are preserved in the analog." See page 10, lines 16-20 of the specification.

Given that the hydrophobicity, net charge at physiological pH, volume, and hydrogen bonding capacities of the parent polypeptide or protein are preserved in the modified analog of the parent polypeptide, one of ordinary skill in the art would expect that the biological activity of the analog would be similar to that of the parent polypeptide. Applicant, therefore respectfully submits that claim 4, is adequately enabled by the specification.

Claims 17 and 18 recite specific pH ranges of an anionic donor reservoir formulation containing the analog set forth in claim 1. The claims specify a pH range "about 3.5 to about 7.4" (claim 17) and a range of "about 5 to about 7.4" (claim 18). The specification clearly discloses that:

> "the pH range of an anodic donor reservoir formulation containing the analog polypeptide is in the pH range of about 3.5 to about 8, and preferably about 5 to 6. At these pH ranges, the replacement of His for Gln, Asn or Thr results in increased hydrophilicity of the analog compared to the parent drug or unmodified polypeptide due to the positive charge on the imidazole ring and increased electrophoretic mobility due to the higher net positive charge." *See* page 8, line 25-31 of the specification.

Furthermore, Examples 1-3 of the specification show that when histidine substituted polypeptides are in a formulation at a pH of 5 or a pH of 6, a positive net charge of the polypeptide is found. Applicants respectfully submit that one of ordinary skill in the art would find that the teachings of the specification clearly enables claims 17 and 18.

Claim Rejections under 35 U.S.C. § 103(a)

Claims 1, 4, 17, and 18 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,205,022 issued to Chien et al. (hereinafter "Chien"), in view of Green et al. (Phar. Research, vol. 8, no. 9, pp. 1121-1127 (1992) (hereinafter "Green") and Markussen et al. (Protein Engin., vol. 2, no. 2, pp. 157-166 (July 1988) (hereinafter "Markussen"). Applicant respectfully submits that claims 1, 4, 17 and 18, as amended, are not rendered obvious by the cited

prior art references, as the Office Action has failed to set forth a *prima facie* case of obviousness with respect to the claims.

Claim 1 of the application, on which claims 4, 17 and 18 depend, has been amended to recite:

> "A method for delivering a pharmaceutical polypeptide agent through a body surface, comprising the steps of:
>
> (a) providing a synthetic analog of a pharmaceutical parent polypeptide agent, wherein the pharmaceutical parent polypeptide agent includes <u>at least one threonine residue</u> and the synthetic analog of the pharmaceutical parent polypeptide agent has <u>at least one threonine residue replaced with histidine</u>; and
>
> (b) delivering the analog through the body surface by electrotransport." See claim 1, emphasis added

Applicant respectfully submits that the cited references, alone or in combination, fail to teach or suggest all of the limitations of amended claim 1. Specifically, none of the cited prior art references teaches the replacement of a threonine residue of a polypeptide with histidine to provide a synthetic analog that is delivered a body surface by electrotransport.

The Chien reference discloses an iontotherapeutic device having two chambers separated by a permselective membrane, with which certain ionized pharmaceuticals, such as insulin, can be delivered. Chien discloses no more than that specific ionizable polypeptide drugs, such as insulin, can be ionized within a particular pH range and be delivered by iontophoresis from a delivery chamber containing a solution of the ionizable drug, wherein the pH of the solution is within that particular range. Thus, Chien teaches the adjustment of pH to aid in the transfer of the polypeptide drugs. The Chien reference contains no teaching or suggestion of the specific modification of any polypeptide to increase the electroflux transport of the polypeptide, let alone the specific modification of threonine for histidine in a polypeptide.

The Green reference discloses the electrotransport characteristics of synthetic tripeptides, one of which includes a histidine residue. The tripeptides studied therein were all of the general formula Ac-Ala-X-Ala-NH($Bu^t$), in which the carboxy and amino termini (both alanine residues (Ala)) were blocked to neutralize the charge of each such terminus, and the central amino acid residue (X) varied. The Green reference, however, does not teach or suggest substituting the amino acid residue histidine for threonine in any polypeptide. Furthermore, Green provides no data comparing the iontophoretic flux of their synthetic tripeptides to the flux of even a single

known peptide or polypeptide agent. Green teaches no more than a greater iontophoretic flux in its positively charged tripeptides when they were delivered from a donor solution as a pH of 4 compared to when the same peptide was delivered from a donor solution at a pH of 7.4.

The Markussen reference discloses the results of a study of the stability of various analogs of insulin, including an analog produced by substituting histidine for a particular glutamine residue of a naturally occurring form of insulin. Markussen states that the histidine-substituted insulin analog was found to be biologically active, and more stable than other analogs studied therein. Markussen does not teach or suggest any substitution of histidine for threonine in a polypeptide. Furthermore, Markussen neither teaches nor suggests that the histidine-substituted analog of insulin described therein would have an enhanced electrotransport flux capacity, as is taught by the present disclosure. In fact, Markussen makes no mention of the electrotransport of peptides, polypeptides, or proteins of any shape or form.

Applicants respectfully submit that none of the cited prior art references, alone or in combination, teach or suggest the substitution of histidine for threonine to provide a synthetic analog that is delivered a body surface by electrotransport. As the references fail to teach all of the limitations of claim 1, the references fail to provide for a *prima facie* case of obviousness with respect to claim 1. Thus, Applicant respectfully requests that the rejection of claim 1 and claims 4, 17, and 18 which depend on claim 1, be withdrawn.

Non-Statutory Double Patenting Rejection

Claims 1, 4, 17-18, and 26-27 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 1-4 and 17-18 of U.S. Patent Application No. 08/466,610 (the '610 application). Applicant submits herewith a terminal disclaimer under 37 C.F.R. § 1.321(c), along with the proper fee, to obviate this rejection. Accordingly, Applicant requests that the rejection be withdrawn.

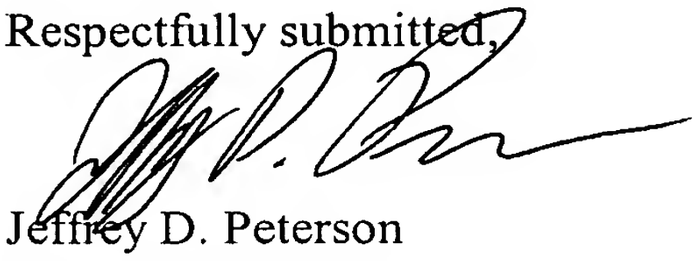
## SUMMARY

Based on the foregoing, Applicant respectfully submits that the present application is in condition for allowance, and a favorable action thereon is respectfully requested. Should the Examiner feel that any other point requires consideration or that the form of the claims can be improved, the Examiner is invited to contact the undersigned at the telephone number listed

below.

The fees for the two-month extension of time and for the terminal disclaimer are enclosed herein. No other fee is believed due in connection with this submission. Please charge any additional fee due to Deposit Account No. 50-0842.

Respectfully submitted,



Jeffrey D. Peterson
Reg. No. 49,038

**File No. 011293-9028-01**
Michael Best & Friedrich LLP
One South Pinckney Street
P.O. Box 1806
Madison, Wisconsin 53701-1806
Phone: (608) 257-3501